

Modeling the 2001 Foot-and-Mouth Epidemic in Uruguay using Geo-referenced Data

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Abstract

Foot-and-Mouth disease (FMD) is a highly infectious illness of livestock and a serious economic threat. We model the 2001 FMD epidemic in Uruguay using an explicit discrete spatial epidemic model (comprising a series of coupled differential equations) that includes geo-referenced data (i.e. euclidean distances between farms, as estimated in relation to distances between county centroids). The value of spatially explicit models in the development and testing of FMD control measures is tested using the corresponding spatially homogeneous model as basis for comparison. The limitations of spatially homogeneous models are illustrated by their inability to capture effectively observed patterns of spread. For the situation of Uruguay, our discrete spatial model captures a double peak in the epidemic, pattern not observed under the spatially homogeneous model. We define internal (within counties) and external (across counties) reproductive numbers, that is, within and across-county contributions to the average number of secondary infections under low levels of local infection. We estimate a mean internal $\bar{R}_0^{in} \approx 280.47$ while the external $\bar{R}_0^{out} \approx 2.64$. Movement restrictions reduced them to $\bar{R}_m^{in} \approx 87$ and $\bar{R}_m^{out} \approx 0.82$. Twelve days after the start of the mass vaccination policy the internal reproductive number dropped to less than one. We explore the expected impact of how quickly mass vaccination is implemented after the start of an outbreak. Our model predicts that if the mass vaccination program had been delayed an additional five days, then there would have been 50% more cases. If the vaccination program had been implemented 5 days prior to the actual date, our model predicts the epidemic would have been reduced by 37%.

Keywords: Foot and Mouth Disease; spatial model; reproductive number; Uruguay; movement restrictions; mass vaccination; differential equations; mathematical model.

1 Introduction

Foot and mouth disease (FMD) is a highly infectious illness caused by an aphthovirus that affects cloven-hoofed animals such as pigs, cattle, and sheep. Infected animals shed large amounts of the virus through the mouth and nose. Viral particles can survive in objects such as shoes, clothes, or vehicle tires. The wind can carry the virus long distances [1]. Typically outbreaks do not reoccur in a region for a long time. For instance, Japan had been FMD free for 92 years until an outbreak was confirmed in 2000 [2] and Great Britain was FMD free for 33 years before the recent epidemic in 2001 [3].

The probability that FMD will cause an epidemic depends on the susceptibility of the livestock where the infectious agent is introduced and the timely response and effectiveness of

interventions. The basic reproductive number, R_0 , is the number of secondary cases generated by a primary case when this is introduced in a population of fully susceptible individuals [4, 6, 5, 7, 8, 9]. That is, R_0 measures the power of a disease to spread under a scenario that facilitates maximal growth (beginning of epidemic). Once an epidemic starts, the number of livestock decreases and control measures are implemented causing the reproductive number $R(t)$ (where $R(0) = R_0$) to decay [10]. The objective of any contingency plan is to make $R(t) < 1$ by identifying effective intervention policies that could be implemented as soon as possible. The high infectiousness characteristic of FMD makes this difficult to achieve [11].

Transmission of FMD can be localized (between adjacent farms [12, 13, 14]). Long distance transmission through daily milk collection, meat transportation, animal movement, etc. are not only possible but extremely likely. Hence, intervention strategies must incorporate spatial heterogeneity [11, 15]. A data-base simulation of the FMD epidemic in Uruguay in 2001 [16] highlights the importance of heterogeneity and geographic variability on the spread of this disease.

The cost of FMD epidemics can be high. For instance, at least 4 million animals were destroyed during the 2001 FMD epidemic in Great Britain [1] and the exportation of animal goods is not permitted for a period of 6-12 months post outbreak. During the 2001 FMD epidemic in Great Britain, two teams of researchers developed highly refined models to aid in the decision-making process [12, 13]. Both teams concluded that a culling policy was the best strategy to control the ongoing FMD epidemic. Their conclusions relied on data that included the location of farms, farm animal density and animal heterogeneity within farms. Longitudinal data on the number of farms infected and the culling process was available [1].

The first case of the 2001 Foot-and-Mouth Disease (FMD) epidemic in Uruguay was reported in the state of Soriano close to the border with Argentina on April 23rd [17, 18]. The epidemic spread through regions where previously it had not existed (exotic disease). This situation and the good geo-referenced data available provides an excellent test bed for the evaluation of a geo-deterministic model. In just a few days, the epidemic had disseminated over the entire country. The epidemic reached its peak incidence of 66 new cases on May 25th and 1763 cases were reported by July 10th, 2001 (Figure 1). Animal slaughter took place from April 25 to April 29 (total: 5,295 cattle; 1,481 sheep; 332 pigs) and on April 27 (4 days after the first reported case) animal movement restrictions were enforced by the police and the army. People movement was never banned (farm personnel continued to come in and out during the

roadblock period). An awareness campaign to farmers via press release and personal visits by veterinarians to farms was implemented. Export controls were implemented in borders, airports and harbors [18].

Mass vaccination (60–70% expected efficacy) started on May 5 with May 28 as the expected completion date. No high potency vaccines (where the protective immunity is reached within 3-4 days [19]) were used. Hence, peak protective levels of the serum antibodies from vaccination were expected to take up to 14-28 days. The vaccination program did not include calves younger than 3 months, pigs or goats. Vaccines were delivered to county/district veterinarians where farmers picked them up and administered them to their own herds. The second round of mass vaccination (booster vaccination with expected 100% efficacy) started on June 15 and was completed on July 22.

We model the 2001 FMD epidemic in Uruguay using a discrete spatial deterministic epidemic model that includes geo-referenced data (i.e. euclidean distances between farms, as estimated in relation to distances between county centroids). Our discrete spatial model is compared to a classical mean-field model. The ability of both models to fit the epidemic incidence data is studied. We estimate epidemiological and control parameters via least-squares fitting. We compute internal (within counties) and external (across counties) reproductive numbers before and after interventions were implemented. The impact of time delays on a mass vaccination policy depending on when (how early/late) it is implemented after an outbreak starts is explored [20].

2 Models

We introduce an explicit discrete spatial deterministic model with interventions. We classify the number of secondary cases generated by a primary case during its entire period of infectiousness as *internal* (within counties) and *external* (across counties). In order to assess the ability of our spatial model to capture observed FMD patterns of spread, we introduce the corresponding spatially homogeneous model as basis for comparison. Since interventions were not implemented from the beginning of the epidemic, control model parameters are time dependent and estimated via least-squares fitting techniques. Standard deviations for the estimated parameters are also provided.

2.1 Spatial epidemic model

We model the FMD epidemic at the level of farms or premises aggregated at the level of counties (Table 1). We classify farms as susceptible (S), latent (L), infectious and undetected (I), and detected and removed (J). A susceptible farm in county i in contact with the virus enters the latent (uninfectious and asymptomatic) class (L) at rate $\sum_{j=1}^n \beta_{ij} I_j$. In other words, the rate of infection is assumed to be directly proportional to the additive effects from all infected farms in all counties j . The transmission rate β_{ij} between farms in counties i and j decays exponentially fast with the euclidean distance of their respective county centroids. The elements of the mixing matrix β_{ij} [21] can be expressed as:

$$\beta_{ij} = \beta_0 e^{-q d_{i,j}}.$$

Here β_0 is the average transmission rate of infectious farms within each county, d_{ij} is the distance between counties i and j as estimated in relation to distances between county centroids (Figure 3), and q quantifies the extent of local spread (or $1/q$ can be interpreted as the FMD mean transmission range). Since $d_{ii} = 0$, we assume uniform mixing within counties. Latent farms progress to the infectious state after a mean time of $1/k$ days and the infectious farms are detected and isolated from the rest at rate α .

The spatial transmission dynamics of Foot-and-Mouth Disease can be modeled by the system of nonlinear ordinary differential equations:

$$\begin{aligned} \dot{S}_i &= -S_i \sum_{j=1}^n \beta_{ij} I_j \\ \dot{L}_i &= S_i \sum_{j=1}^n \beta_{ij} I_j - k L_i \\ \dot{I}_i &= k L_i - \alpha I_i \\ \dot{J}_i &= \alpha I_i. \end{aligned} \tag{1}$$

The dot denotes time derivatives where S_i , L_i , I_i , and J_i denote the number of susceptible, latent, infectious, and removed/isolated farms in each county i ($i = 1, 2, \dots, n$). The distribution of the number of farms in the different counties is given in Table 1.

Our spatially dependent transmission rate β_{ij} is analogous to the patch connectivity index in the context of metapopulation dynamics [22, 23] where d_{ij} could be some measure of the influence of the landscape on migration [24]. The elements of $\{d_{ij}\}$ could be used as an “index” that could incorporate wind direction and animal heterogeneity within farms (dairy, beef, etc.). Here, we assume that the county connectivity d_{ij} is well approximated by the distance between

counties.

Unfortunately, we do not know an analytical expression for R_0 for our multi-county model (1). However, we can numerically compute the basic reproductive number using model parameter estimates [8]. We define the *internal* (within counties) basic reproductive number of county i , $R_{0_i}^{in}$, as the number of secondary cases generated by a primary case in county i within the same county and is given by $R_{0_i}^{in} = \beta_0 N_i / \alpha$. Similarly, we define the *external* (across counties) basic reproductive number of county i , $R_{0_i}^{out}$, as the number of secondary cases generated by a primary case in county i in any other county j where $j \neq i$ and is given by $R_{0_i}^{out} = \sum_{j \neq i}^n \beta_0 N_j e^{-qd_{ij}} / \alpha$.

2.2 Spatial epidemic model with interventions

Our model (see compartment diagram in Figure 4) with interventions is given by the system of nonlinear ordinary differential equations:

$$\begin{aligned}
\dot{S}_i &= -S_i(t) \sum_{j=1}^n \beta_{ij}(t) I_j(t) - \nu(t) S_i(t) \\
\dot{V}_i &= \nu(t) S_i(t) - V_i(t) \sum_{j=1}^n \beta_{ij}(t) I_j(t) - \mu(t) V_i(t) \\
\dot{L}_i &= (S_i(t) + V_i(t)) \sum_{j=1}^n \beta_{ij}(t) I_j(t) - k(t) L_i(t) \\
\dot{I}_i &= k(t) L_i(t) - \alpha(t) I_i(t) \\
\dot{J}_i &= \alpha(t) I_i(t) \\
\dot{P}_i &= \mu(t) V_i(t)
\end{aligned} \tag{2}$$

where susceptible farms in county i (S_i) are vaccinated at rate ν (V_i). Vaccinated farms in V_i enter the protected class P_i at rate μ . Vaccinated farms in county i that have not yet reached protective levels (class P) in contact with the virus enter the latent (uninfectious and asymptomatic) class (L) at rate $\sum_{j=1}^n \beta_{ij} I_j$. The total cumulative number of reported infected farms as a function of time is given by $C(t) = \sum_{i=1}^n J_i(t)$ and the daily number of new reported infected farms is given by $\dot{C}(t)$.

The government imposed movement restrictions (the first intervention implemented) five days after the first reported infected farm. After movement restrictions, the *internal* and *external* reproductive numbers of county i became $R_{m_i}^{in} = \beta N_i / \alpha$ and $R_{m_i}^{out} = \sum_{j \neq i}^n \beta N_j e^{-qd_{ij}} / \alpha$. The second type of interventions consisted of a mass vaccination program that started nine days after movement restrictions were implemented. The reproductive number that considers the effects of the mass vaccination program after movement restrictions can be defined as a function of the effective time T elapsed from the beginning of mass vaccination at time t_v to time t .

That is, $T = t - t_v - 1/\mu$ where $1/\mu$ is the mean time it takes vaccinated farms to reach protective antibody levels. The *internal* and *external* reproductive numbers can be estimated using $R(T)_i^{in} = (\beta N_i / \alpha) s_i^*$ and $R(T)_i^{out} = (\sum_{j \neq i}^n \beta N_j e^{-qd_{ij}} s_j^* / \alpha)$ where $i = 1, 2, \dots, n$ counties and $s_i^* = \begin{cases} 0 & N_i \leq T\nu \\ 1 - T\nu/N_i & N_i > T\nu \end{cases}$.

The parameters $\beta(t)$, $\alpha(t)$, $\nu(t)$, and $\mu(t)$ depend on time since control measures cannot be implemented simultaneously but rather at different times during the epidemic:

$$\beta(t) = \begin{cases} \beta_0 & t < \tau_m \\ \beta & t \geq \tau_m \end{cases}$$

$$\alpha(t) = \begin{cases} \alpha_0 & t < \tau_v \\ \alpha & t \geq \tau_v \end{cases}$$

$$\nu(t) = \begin{cases} 0 & t < \tau_v \\ \nu & t \geq \tau_v \end{cases}$$

$$\mu(t) = \begin{cases} 0 & t < \tau_v \\ \mu & t \geq \tau_v \end{cases}$$

Here τ_m (27 April 2001) is the time at which movement restrictions were put in place and τ_v (05 May 2001) is the time at which mass vaccination started.

2.3 Spatially homogeneous model

We will assess the advantage of including spatial heterogeneity to capture observed FMD patterns of spread by comparing prediction with a corresponding spatially homogenous model which considers a uniform transmission rate between farms. That is, $\beta_{ij} = \hat{\beta}(t)$ where

$$\hat{\beta}(t) = \begin{cases} \hat{\beta}_0 & t < \tau_m \\ \hat{\beta} & t \geq \tau_m \end{cases}$$

The system of nonlinear ordinary differential equations becomes [4, 6, 9]:

$$\begin{aligned}
\dot{S}(t) &= -\beta(t)S(t)I(t)/N - \nu S \\
\dot{V}(t) &= \nu S - \beta(t)V(t)I(t)/N - \hat{\mu}V \\
\dot{L}(t) &= \beta(t)(S(t) + V(t))I(t)/N - \hat{k}L(t) \\
\dot{I}(t) &= \hat{k}L(t) - \hat{\alpha}I(t) \\
\dot{J}(t) &= \hat{\alpha}I(t) \\
\dot{P}(t) &= \hat{\mu}V(t)
\end{aligned} \tag{3}$$

where $S(t)$, $V(t)$, $L(t)$, $I(t)$, $J(t)$, and $P(t)$ denote the number of susceptible, vaccinated, latent, infectious, removed/isolated, and protected farms at time t , respectively. The parameters $\alpha(t)$, $\nu(t)$, and $\mu(t)$ depend on time in the same manner as in our explicit spatial model.

3 Epidemiological and control parameters

We use the inter-county distances (i.e. euclidean distances between farms, as estimated in relation to distances between county centroids) as a measure of the connectivity between counties. The epidemic-curve data on the number of cases reported over time identified by counties were obtained from geo-referenced case reports. We estimate epidemiological and control parameters from the cumulative number of infected farms by a least-square fit.

3.1 Spatial and epidemic data

We grouped the 19 Uruguayan states into three contiguous regions (Region I, II and III) in the map of Uruguay (Figure 2 b). Table 1 shows the distribution of the number of counties per state and the mean density of farms per county in each Uruguayan state. Figure 3 shows the distribution of all the inter-county distances. Using geo-referenced case reports obtained from public records of the Uruguayan Ministry of Livestock, Agriculture, and Fisheries (MGAP), the Pan-american Health Organization, and the World Organization for Animal Health (OIE) [25, 26, 27], we generate a table of the number of daily new reported infected farms during the first 79 days of the epidemic. That is, a table of the form (t_i, x_i) , $i = 1, \dots, 1763$ where t_i denotes the time and x_i the location of the i^{th} reporting infected farm. Each infected farm can be associated geographically to a region, state, and county. Table 2 shows that the focus of the epidemic was in region I where the epidemic started (57% of total infected farms) which includes states of Soriano (26%), Colonia (21%) and Rio Negro (10%).

It has been recently shown experimentally in pigs and cattle that the rate of spread, the incubation period, and the severity of disease depend on the dose received, the route of introduction, the animal species and husbandry conditions [28]. These factors are not independent. For example, the dose received is correlated to the length of the incubation period. The FMD virus is excreted up to 11 days once symptoms appear [29]. The incubation period for FMD has been reported to be between 3 – 6 days with a maximum of 14 days [30, 31, 32]. A recent experimental study in cattle reports the presence of viral RNA (mouth and nasal swabs) in all infected cattle within 24 h post infection and peak levels were reached 1 – 2.5 days post infection. In some animals viral RNA was not detected until 7 – 18 days post infection [33]. Latent animals progress to an infectious state that lasts for about 8 days. Animals are asymptomatic during the first 5 days of the infectious period [12]. The remaining 3 – 5 days (symptomatic and infectious) [33] is the time that it takes on average to detect and remove/isolate the infected animals from the rest. Most animals recover with reduced weight gain or milk yield [13] .

3.2 Parameter estimation

The model parameters $\Theta = (\beta(t), k(t), \alpha(t), q(t), \nu(t), \mu(t))$ are estimated from the cumulative number of reported farms (t_i, y_i) where t_i denotes the i^{th} reporting time (79 reporting days) and y_i is the cumulative number of reported farms by least-square fitting to $C(t, \Theta)$ in Region I (where the outbreak started and the majority of cases occurred). This gives a system of 5 (equations per county) * 42 (counties in region I) = 210 differential equations. Farm density of each county is given in Table 1. We wrote a MATLAB program (The MathWorks, Inc.) to carry out the least squares fitting procedure with appropriate initial conditions ($0 < \beta < 100$, $1/5 < k < 1/3$, $1/12 < \alpha < 1/4$, $0 < q < 10$, $0 < \nu < 10$, $0 < \mu < 10$).

The asymptotic variance-covariance $AV(\hat{\theta})$ of the least-squares estimate using a Brownian bridge error structure to model the stochastic temporal dependence of the cumulative number of cases is

$$AV(\hat{\theta}) = \sigma^2 \mathbf{B}(\Theta_0) \nabla C(\Theta_0)^T \mathbf{G} \nabla C(\Theta_0) \mathbf{B}(\Theta_0),$$

where $\mathbf{B}(\Theta_0) = [\nabla C(\Theta_0)^T \nabla C(\Theta_0)]^{-1}$. An estimate of which is

$$\hat{\sigma}^2 \hat{\mathbf{B}}(\hat{\Theta}) \nabla \hat{C}(\hat{\Theta})^T \mathbf{G} \nabla \hat{C}(\hat{\Theta}) \hat{\mathbf{B}}(\hat{\Theta}),$$

where $\hat{\mathbf{B}}(\hat{\boldsymbol{\Theta}}) = [\nabla \hat{\mathbf{C}}(\hat{\boldsymbol{\Theta}})^T \nabla \hat{\mathbf{C}}(\hat{\boldsymbol{\Theta}})]^{-1}$, \mathbf{G} is an $n \times n$ matrix such that $G_{i,j} = (1/n) \min(i, j) - (ij)/n^2$, n is the total number of observations, $\hat{\sigma}^2 = 1/(I_{1 \times n} \mathbf{G} I_{n \times 1}) \sum (y_i - C(t_i, \hat{\boldsymbol{\Theta}}))^2$, and $\nabla \hat{\mathbf{C}}$ are numerical derivatives of $C(\hat{\boldsymbol{\Theta}})$. The error structure [34] is modeled by a Brownian bridge (\mathbf{G}) to account for the stochastic temporal dependence of the cumulative number of cases. That is, G captures the higher variability in the cumulative number of cases observed on the middle course of the epidemic and the smaller variability observed at the beginning and the end of the epidemic.

4 Results

The initial intrinsic growth rate r (assuming initial exponential growth rate $y \propto e^{rt}$) is 0.65, 0.35, and 0.19 for Regions I, II, and III, respectively (Figure 2 b). These growth rates decayed as awareness of the epidemic increased and enforced movement restrictions (epidemic started to spread from Region I onwards) became more established. After 07 May 2001 the rate of growth was about the same in all three regions (see Figure 2 a). To reduce the model complexity, we analyze the case incidence data of Region I where the majority of cases occurred (57% of total cases).

The non-spatial epidemic model (3) fit to the cumulative number of infected farms shows a systematic deviation from the epidemic data during the first 20 days of the epidemic (Figure 5). The model parameter estimates are given in Table 3. We then fit the cumulative number of reported farms in Region I using our spatial model with interventions (2). Our model agrees well with the data (Figure 6) and the parameter estimates are in agreement with FMD epidemiology (see Table 4). Furthermore, our model predicts a two-peak epidemic with the second peak being of higher amplitude. We explain such dynamics by sparks of infection reaching pockets of susceptible farms [12].

The “free course” of the epidemic occurs in the first 5 days of the epidemic, after which movement restrictions were rapidly enforced by the police and the army. Hence, parameter estimates of the transmission rate and the infectious period during the initial “free” growth of the epidemic could be somewhat uncertain. Our estimate of the transmission rate (β_0) before movement restrictions is 0.33 (SD 0.13) per farm per day compared to our estimate $\beta = 0.10$ (SD 0.03) per farm per day after movement restrictions were put in place. The rates of identification isolation of infected farms before and after movement restrictions were put in place

$(\alpha_0 = 0.14 \text{ (SD 0.02)}, \alpha = 0.14 \text{ (SD 0.02)})$ are not statistically different.

We estimate the basic reproductive number ($R_0 \approx 355$) from model (1) following van den Driessche & Watmough [8] approach that uses the difference of the rate of inflow of new infections in compartment j (f_j) and the inflow and outflow rates in compartment j by all other epidemiological processes (v_j). This large estimate of R_0 reflects the explosive rate at which FMD can spread without interventions. We explain the difference between the internal and external estimates of the reproductive number by the exponential decay with inter-county distance of the transmission rates.

The average *internal* and *external* basic reproductive numbers $\bar{R}_0^{in} \approx 280.47$ and $\bar{R}_0^{out} \approx 2.64$ respectively before movement restriction were enforced. The movement restrictions reduce the reproductive numbers to $\bar{R}_m^{in} \approx 87.20$ and $\bar{R}_m^{out} \approx 0.82$.

After mass vaccination started, our model predicts that the *internal* basic reproductive number rapidly decreased to a number less than one on day 25 (16 May 2001) of the epidemic.

Our estimate of the vaccination rate of susceptible farms (ν) is 0.25 (SD 0.09) per day. That is, we estimate a mean time of approximately 4 days before a susceptible farm was successfully vaccinated. Vaccination does not provide instantaneous protection against FMD. Our estimate for the rate at which vaccinated farms reach protective antibody levels (μ) is 0.14 (SD 0.03) per day. That is, we estimate 7.14 days before successfully vaccinated farms became protected. Our spatial model predicts that the mass vaccination program implemented during the 2001 FMD epidemic in Uruguay reduced the final epidemic size to 1003 infected farms in Region I compared to 5251 (98.5% of all the farms in Region I) if no mass vaccination had been implemented after movement restrictions (multiple outbreaks are observed, Figure 7). A 5-day delay in onset of mass vaccination with respect to the actual implementation date yields 1501 (50% increase in the final epidemic size) infected farms. Moreover, if the vaccination program had been implemented 5 days prior to the actual date, our model predicts only 629 (a 37% decrease from the actual epidemic size) infected farms (Figure 7). The sensitivity of the final epidemic size to the time of starts of the mass vaccination program is shown in Figure 8.

We quantify the extent of inter-county spread through the parameter q . Small values of q lead to widespread influence, whereas large q supports local spread. Our estimate for q is 1.03 1/Km (SD 0.10). That is, our estimate of the mean transmission range ($1/q$) is approximately

0.97 Km.

5 Discussion

Mathematical models have played an important role in the decision-making process in the control of FMD epidemics and its economic consequences [3, 13, 12, 35, 36, 37, 38, 39, 40]. During the 2001 FMD epidemic in Great Britain, different approaches were used and included “moment closure” technique [13] and stochastic models [12, 35]. Here, we model the 2001 FMD epidemic in Uruguay using a deterministic model that takes into account the distance among counties in the transmission process (Figure 3), farm density within counties (Table 1) and information on the intervention strategies that were put in place during the outbreak.

The ability of our spatial deterministic model to effectively capture epidemic patterns of spread of FMD is tested using the corresponding spatially homogeneous model as basis for comparison (3). Our spatial model differed with the non-spatial model in: a) non-spatial model fit to the data shows a systematic deviation from epidemic data during the initial epidemic take-off and b) our spatial model displays a double peak in the time series of the daily number of infected farms, pattern not observed under the non-spatial model. We assume that the spatial location of farms play an important role in the transmission dynamics of FMD as a first order approximation. As most models for FMD, our model do not include *road density* considerations but could be incorporated if such data become available. Road density could play a significant role in capturing higher resolution epidemic patterns within states or counties as this measure can be highly heterogeneous among counties. We did not incorporate farm heterogeneity (i.e dairy, beef, etc) in the transmission process [41] but could be considered as well if appropriate data become available. Notwithstanding the relatively basic aspects of FMD transmission considered here, our model is able to capture regional patterns of the 2001 Uruguay FMD epidemic.

By fitting our model to epidemic-curve data on the cumulative number of reported farms, we are able to estimate relevant epidemiological parameters including the average transmission rate within counties (before and after movement restrictions were put in place) (β_0 , β), the incubation period ($1/k$), the infectiousness period (before and after movement restrictions were put in place) ($1/\alpha_0$, $1/\alpha$), and control parameters: mean time before susceptible farms are vaccinated ($1/\nu$) and the mean time it takes for vaccinated farms to achieve protective antibody levels ($1/\mu$). Epidemiological and control parameter estimates are given in Table 4. We observe a reduction by a factor of 3 in the transmission rate before and after movement restrictions

were enforced (Table 4). However, we find no difference between the infectious period before and after movement restrictions were implemented.

Our spatial epidemic model captures a two-peak outbreak in the transmission dynamics of the 2001 FMD epidemic in Uruguay (Figure 6). These patterns of spread cannot be reproduced using fully mixed systems. In our spatial model, such dynamics arise from long distance sparks of infection, which can trigger secondary outbreaks. Moreover, secondary “peaks” of infection can be of higher intensity as in the 2001 FMD epidemic in Uruguay (Figure 6).

Our estimate of the basic reproductive number ($R_0 \approx 355$) is large and this can be explained by the spatial transmission parameter that dominate the course of FMD epidemics. The basic reproductive number for spatial models must be much higher for epidemics to occur [42] because of the more localized transmission dynamics. Woolhouse et al. (1996) [43] report a basic reproductive number for an FMD-infected animal to be between 2 and 73. Our R_0 estimates are given in terms the number of secondary infected farms generated by a primary infectious farm during its infectious period in a fully susceptible landscape.

More useful information can be obtained by looking at the number of secondary cases generated within counties and between counties. Before movement restrictions were imposed, the average number of secondary cases generated externally to counties (*external* basic reproductive number) was $\bar{R}_0^{out} \approx 2.64$. However, once movement restriction had been enforced on 27 April 2001, the average number of external secondary cases declined to a number less than one ($\bar{R}_m^{out} \approx 0.82$) which indicates that once movement restrictions had been put in place, the transmission process was mostly confined to within counties with rarely long distance (at the level of counties) transmission events. This drop in the reproductive number is in agreement with the reduction of the intrinsic growth rate r observed in the data (Figure 2 a). This is also supported by our parameter estimate $1/q = 0.97$ (Km) characterizing the extent of local spread or the average transmission range of the disease under the assumption of uniform mixing of farms within counties. We estimate that the reproductive number within counties decayed to a number less than one approximately 12 days after the mass vaccination program started.

Our model predicts a reduction in the final epidemic size of 374 infected farms in Region I (see Figure 7 b) if mass vaccination had started 5 days prior to the actual date. Moreover, our model predicts no secondary “peaks” of infection of higher intensity under this scenario (Figure 6) which can be explained by the higher number of vaccinated farms achieved by starting mass

vaccination earlier. A 5-day delay in its implementation had generated 498 more cases (Figure 7). This highlights the effects of delays in the implementation of control measures, which are tightly linked to the economic impact of the epidemic. Figure 8 shows the sensitivity of the final epidemic size in Region I to the time of start of mass vaccination.

There is only few data on the different aspects of the vaccine and the vaccination program including the vaccination coverage (since not all the susceptible animals are vaccinated for several reasons) and the vaccine efficacy, which can be very different from the one observed in the field. During the epidemic, young calves were not vaccinated (< 3 month-olds). Pigs and sheep were neither vaccinated [18]. The vaccine utilized for the mass vaccination program was specific. That is, the vaccine targeted to the virus observed during the FMD epidemic (virus type A_{24} [18]). The age, health, and stress of the livestock influence the animal’s response and the effectiveness of the vaccine (the “responders” index). Furthermore, some animals do not reach protective antibody levels from those who generate immune response. For the 2001 FMD epidemic in Uruguay, we estimate 7.14 days for successfully vaccinated farms to reach antibody protective levels.

6 Conclusions

- FMD epidemic models incorporating spatial structures can capture regional patterns of spread
- Long distance sparks of infection reaching areas of susceptible farms can generate multiple peaks in the global infection rates. In contrast to spatially structured models, spatially homogeneous models are unable to reproduce such patterns of infection
- Our model predicts the basic reproductive number will rapidly decrease after movement restrictions are imposed. This observation agrees with the rapid decrease in the intrinsic growth rate observed in the incidence data (Figure 2 a)
- There was a rapid drop in the external reproductive number to less than one after movement restrictions were enforced. Following these restrictions, transmissions were localized and there was a very low probability for long-range transmission events. Hence, ensuring that movement restrictions are strictly enforced is crucial in any contingency plan against FMD

- Mass vaccination implemented along with a policy of movement restrictions is an effective means of control and significantly reduces the final epidemic size.
- The 2001 FMD Uruguayan epidemic data and analysis can be used for comparison when assessing other control measures such as culling policies and higher potency vaccines implemented alone or in combination with other interventions.

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Tables & Figures

Region I			Region II			Region III		
State	Counties	N_j	State	Counties	N_j	State	Counties	N_j
Soriano	12	140	Paysandu	13	121	Artigas	12	118
Colonia	18	151	Salto	16	111	Rivera	10	206
Rio Negro	13	71	S. Jose	10	243	C. Largo	14	196
			Flores	9	91	Lavalleja	14	235
			Florida	16	152	Rocha	12	190
			Tacuarembó	16	152	T. y Tres	11	163
			Durazno	15	136	Maldonado	13	136
						Canelones	27	141

Table 1: Distribution of the number of counties per state and the average number of farms per county (N_j).

Region I			Region II			Region III		
State	Infected	Total	State	Infected	Total	State	Infected	Total
Soriano	463	1682	Paysandu	64	1567	Artigas	34	1421
Colonia	362	2724	Salto	56	1783	Rivera	14	2064
Rio Negro	178	925	S. Jose	68	2430	C. Largo	26	2744
			Flores	62	816	Lavalleja	15	3296
			Florida	109	2436	Rocha	12	2284
			Tacuarembó	111	2427	T. y Tres	59	1797
			Durazno	92	2043	Maldonado	12	1773
						Canelones	25	3800
Overall Total	1003	5331		562	13502		198	19179

Table 2: Distribution of the total number of infected farms among the different Uruguayan states within each defined contiguous region.

Params.	Definition	Estim.	SD
$\hat{\beta}_0$	Average transmission rate between farms <i>before</i> mov. restrictions	0.77	0.04
$\hat{\beta}$	Average transmission rate between farms <i>after</i> mov. restrictions	0.49	0.08
$\hat{\alpha}_0$	Rate of removal from infectious state <i>before</i> mov. restrictions	0.16	0.07
$\hat{\alpha}$	Rate of removal from infectious state <i>after</i> mov. restrictions	0.14	0.02
\hat{k}	Rate of progression from latent to infectious state	0.26	0.07
$\hat{\nu}$	Vaccination rate of susceptible farms	0.16	0.04
$\hat{\mu}$	Rate at which vaccinated farms achieve protective levels	0.31	0.05

Table 3: Parameter definitions and estimates obtained from least-squares fitting of the non-spatial epidemic model (3) to the cumulative number of infected farms over time (days) in Region I (Figure 5). All the parameters have units 1/ days.

Params.	Definition	Estim.	SD
β_0	Average transmission rate within counties <i>before</i> mov. restrictions	0.33	0.13
β	Average transmission rate within counties <i>after</i> mov. restrictions	0.10	0.03
α_0	Rate of removal from infectious state <i>before</i> mov. restrictions	0.14	0.02
α	Rate of removal from infectious state <i>after</i> mov. restrictions	0.14	0.02
k	Rate of progression from latent to infectious state	0.28	0.05
q^*	Positive constant quantifying the extent of local spread	1.03	0.10
ν	Vaccination rate of susceptible farms	0.25	0.09
μ	Rate at which vaccinated farms achieve protective levels	0.14	0.03

Table 4: Parameter definitions and estimates obtained from least-squares fitting of the spatial epidemic model (2) to the cumulative number of infected farms over time (days) in Region I (Figure 6). All the parameters have units 1/ days except for q whose units are 1/Km. * Small values of q lead to widespread influence, whereas large q supports local spread. Great mobility and frequent interactions among farms would lead to small values of q .

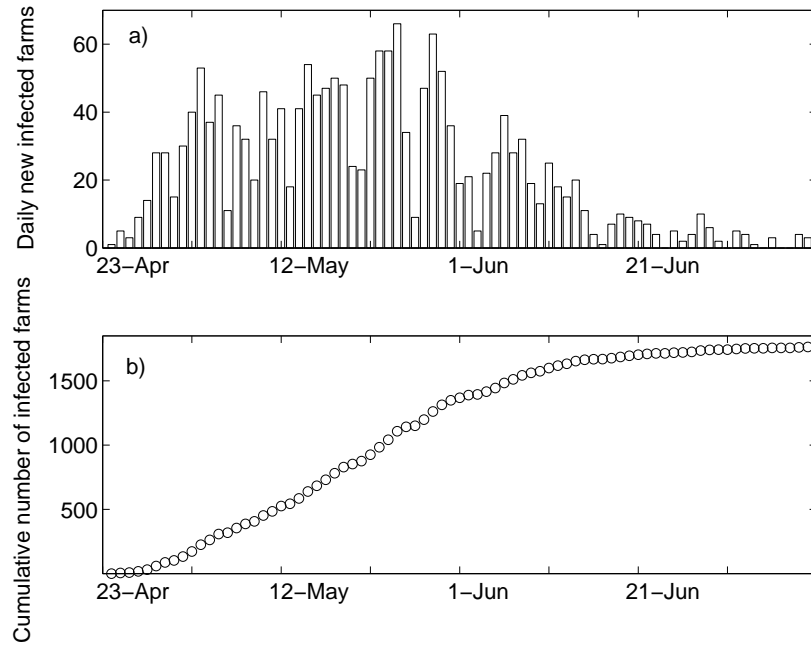


Figure 1: a) Daily and b) cumulative number of reported infected farms during the 2001 Foot and Mouth Disease in Uruguay. The epidemic reached its maximum of 66 cases on day 33 (25 May 2001). 1763 cases had been reported by day 79 (10 July 2001). Data has been taken from refs. [25, 26, 27]. The periodic dips in the data are due to low reporting rates on the weekends.

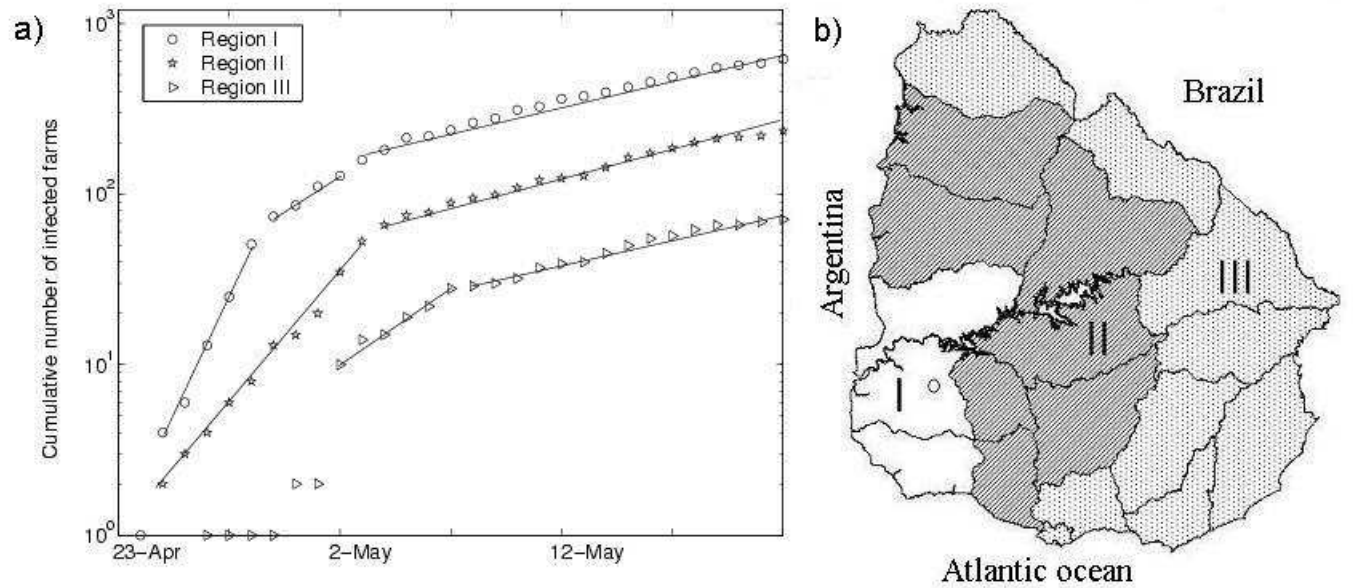


Figure 2: a) The initial intrinsic growth rate r in Region I, II and III are 0.65, 0.35, and 0.19 respectively ; b) Region I, II and III comprise 3, 7 and 8 Uruguayan states respectively (see Table 2). We estimate the intrinsic growth rate in region III using the cumulative number of cases from 02 May to 07 May 2001 due to underreporting of number of cases before 02 May 2001. The intrinsic growth rate after 07 May 2001 is approximately the same in the three regions once movement restrictions and some depletion in the number of susceptible farms had taken place. Mass vaccination started on 05 May 2001.

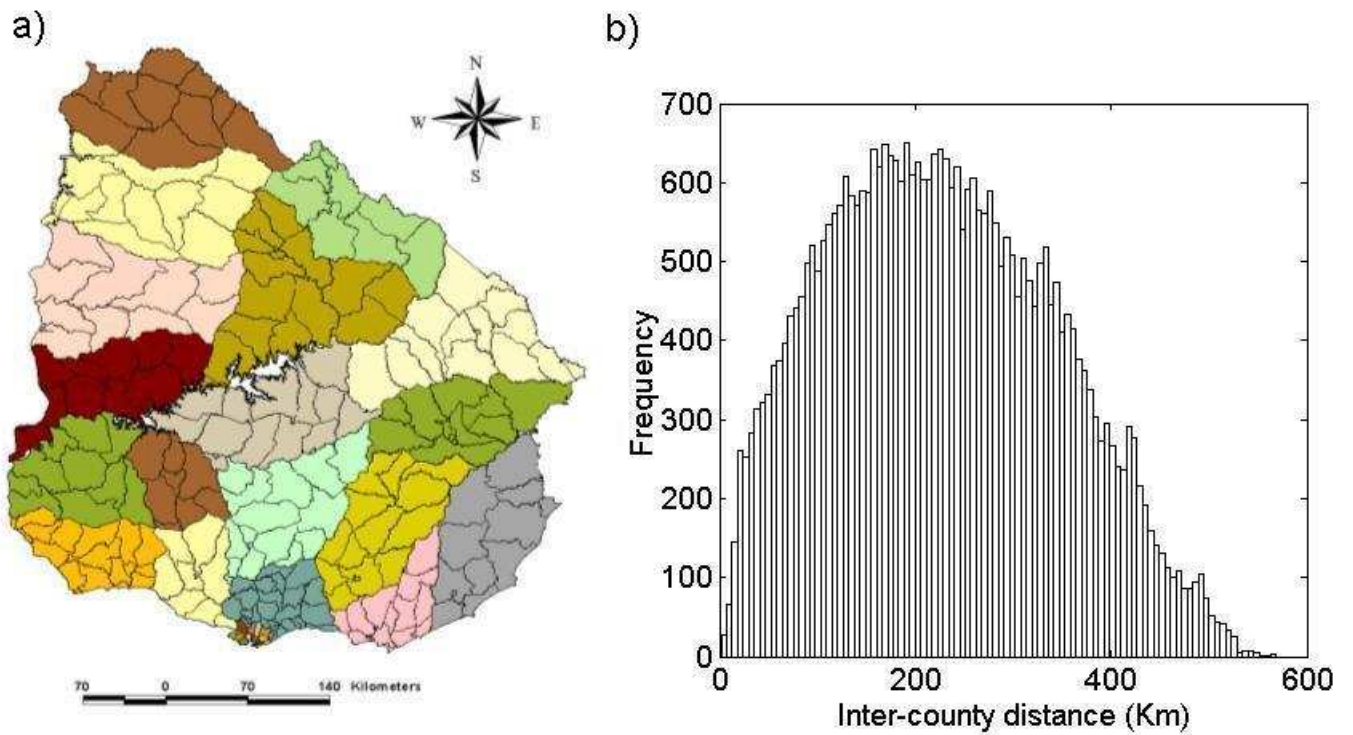


Figure 3: a) Map of Uruguay with state (color) and county divisions; b) distribution of inter-county (euclidean) distances which were obtained using a geographic information system (GIS). The centroid of each county is used to compute euclidean distances.

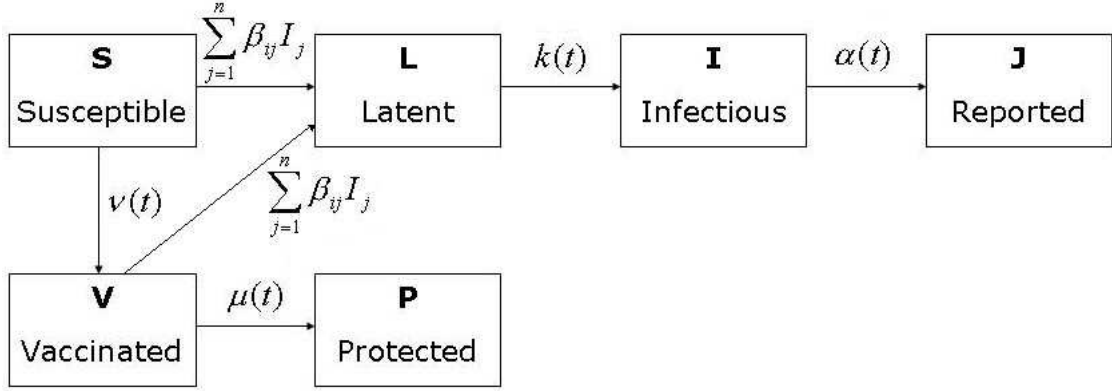


Figure 4: Schematic representation of the state progression of farms in a given county. Susceptible farms become infected at rate $\sum_{j=1}^n \beta_{ij} I_j$ and progress to the latent class. That is, the rate of infection is assumed to be directly proportional to the additive effects from all infected farms in all counties as explained in the text. Latent farms progress to the infectious state after a mean time of $1/k$ days and the infectious farms are detected at rate α . Movement restrictions ($t \geq \tau_m$) are modeled as a reduction in the mean transmission rate within counties. That is, we assume that the mean transmission rate within counties decayed from β_0 to β after movement restrictions were enforced. Once the mass vaccination program started ($t \geq \tau_v$), susceptible farms (S) were vaccinated at rate ν . Vaccinated farms (V) become protected (P) at rate μ .

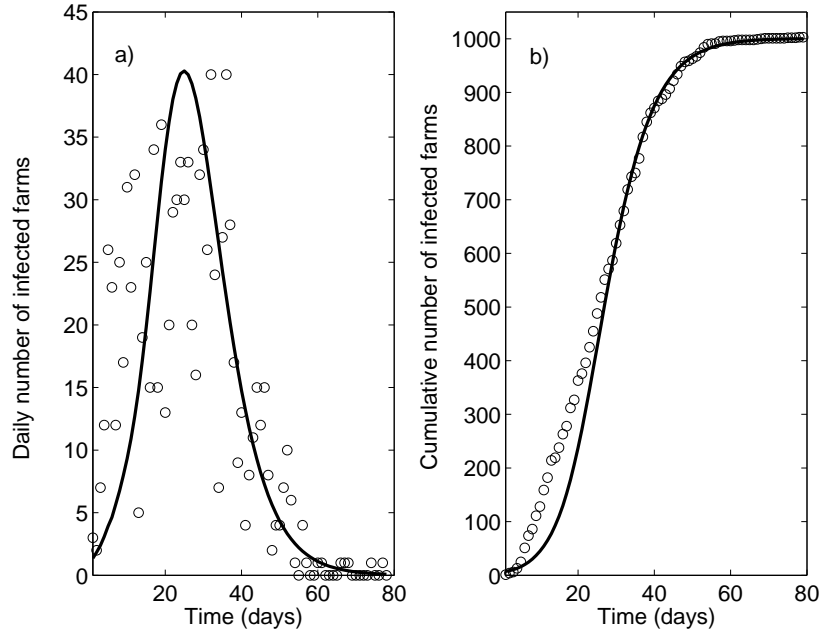


Figure 5: a) The daily and b) cumulative number of reported infected farms in Region I (Figure 2) where the outbreak started (23 April 2001) and focused (57% of cases). Movement restrictions were implemented on 27 April 2001 and mass vaccination started on 05 May 2001. Circles are the data and the solid line is the best-fit solution of the deterministic model equations of the nonspatial model (3) to the data via least squares fitting (parameter estimates are given in Table 3).

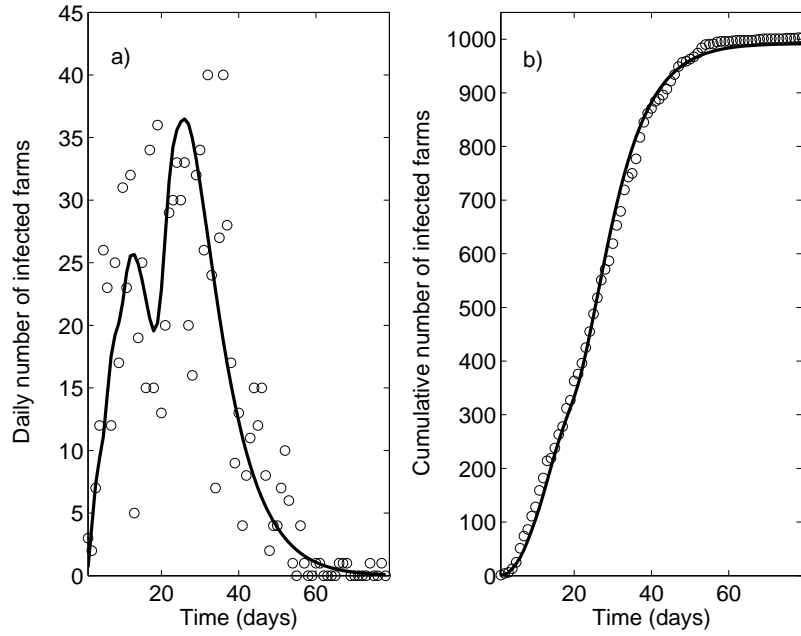


Figure 6: a) The daily and b) cumulative number of reported infected farms in Region I (Figure 2) where the outbreak started (23 April 2001) and focused (57% of cases). Movement restrictions were implemented on 27 April 2001 and mass vaccination started on 05 May 2001. Circles are the data and the solid line is the best-fit solution of the deterministic model equations of the spatial model (2) to the data via least squares fitting (parameter estimates are given in Table 4).

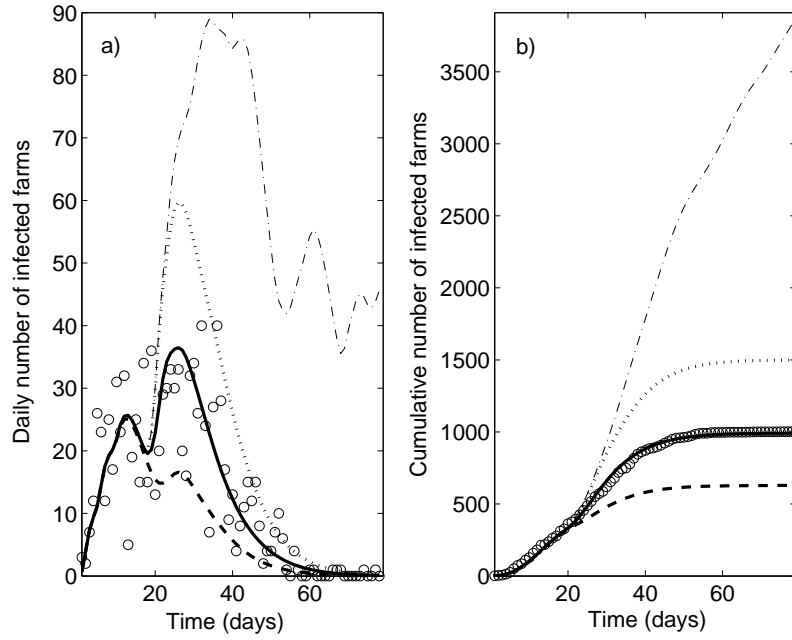


Figure 7: a) The daily and b) cumulative number of reported infected farms in Region I (Figure 2) where the outbreak started (23 April 2001) and focused (57% of cases). Movement restrictions were implemented on 27 April 2001 and mass vaccination started on 05 May 2001. Circles are the data and the solid line is the best-fit solution of the deterministic model equations (2) to the data via least squares fitting (parameter estimates are given in Table 4). Three scenarios are shown: (dash-dot) no mass vaccination implemented after movement restrictions (total of 5252 cases); (dot-dot) mass vaccination with a 5-day delay (1551 cases) and (dash-dash) 5 days before the actual date at which mass vaccination started (604 cases).

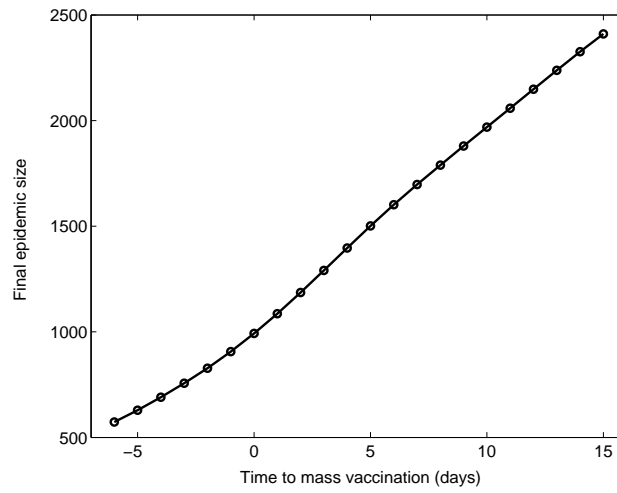


Figure 8: Sensitivity of the final epidemic size (Region I) to the time of start of the mass vaccination program. Negative numbers represent number of days before the actual reported start of the mass vaccination progrme (05 May 2001) while positive numbers represent a delay (days).